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(005316 EXCERPT)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic feeding 82-1 (rat) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 073980

TEST MATERIAL: (RS)-alpha-cyano-3-phenoxybenzyl, (1RS), cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl cyclopropane carboxylate

SYNONYMS: PP321, Karate (substituent of Cyhalothrin, Grenade)

STUDY NUMBER(S): PRO584

REPORT NUMBER: CTL/P/1045

SPONSOR: ICI PLC, Plant Protection Division, Jealott's Hill, Bracknell, UK

TESTING FACILITY: ICI PLC Cntrl. Tox. Lab, Alderly Park, Macclefield, UK

TITLE OF REPORT: PP321: 90 Day Feeding Study in Rats

AUTHOR(S): Hart D, Banham PB, Chart IS, Evans DP, Gore CW, Stonard MD, Moreland S, Godley MJ, Robinson M.

REPORT ISSUED: 2/14/85

IDENTIFYING VOLUME: Volume II, Book 1, Section C, Tab 8C

CONCLUSION: The NOEL is 50 ppm and the LOEL is 250 ppm based on reduction in in body weight gain.

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

PP321 was supplied by ICI PLC, Plant Protection Division, Bracknell, Berkshire, UK. The purity was 96.5% w/w and the reference #'s were: CTL ref. # YO2537/001/005 and batch P13. The chemical was supplied as a buff solid.

Animals:

One hundred male and female SPF Alk/AP Wistar-derived rats were obtained from the Animal Breeding Unit at ICI PLC, Alderly Park. All rats were approximately 21 days old when transported. Twenty rats per sex were assigned to each dose level: 0, 10, 50 and 250 ppm.

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Protocol:

All animals were maintained on the appropriate experimental diet for 90 days. Animals were examined pre-experimentally and once daily for abnormalities in clinical condition and/or behavior. Detailed clinical observations were conducted when the animals were weighed. Bodyweights were recorded immediately before the start of the experiment and once weekly thereafter. Food consumption was also recorded once weekly. Ten animals of each sex per group were selected for blood sampling. Samples were taken from the tail vein prior to the start of the experiment and at 4 weeks into the experiment. Blood was removed from these same animals at termination via cardiac puncture. The following hematological measurements were taken:

hemoglobin, hematocrit, red cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total white cell count, platelet count, differential white cell count and kaolin-cephalin and prothrombin times (at termination only).

Clinical chemistry measurements were taken on ten other male and female animals per group at the same predesignated times as the hematological measurements. The following measurements were taken:

plasma alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), triglycerides, plasma cholesterol, urea, glucose, albumin and total protein.

Urine samples were taken from the same animals from which the clinical chemistry measurements were taken, at the same predesignated times. The samples were collected over an 18 hour period. The following measurements were taken: volume, pH, specific gravity, protein, glucose, ketones and urobilinogen. During the week prior to termination, the eyes of the animals from the control and 250 ppm groups were examined using a Fison's binocular indirect ophthalmoscope.

At termination, all animals were given a full post mortem examination. The following organs were weighed: gonads (combined), spleen, adrenals (combined), kidneys (combined), liver, heart, lungs (combined with trachea attached) and brain. Tissues from the following list were removed from the high dose animals and controls and examined histopathologically together with liver, kidneys, lungs and any abnormal tissues from the lower dose groups:

adrenal glands, aorta, bladder, bone (left femur) including knee joint, brain, cecum, cervical lymph node, cervix, colon, duodenum, epididymis (L+R), eyes (+ Harderian gland), heart, jejunum, ileum, kidneys, lung, liver, mammary gland (female only (x2 inguinal)), mesenteric lymph nodes, esophagus, ovaries, pancreas, pituitary gland, prostate, rectum, salivary glands, sciatic nerves (L+R), seminal vesicles, skin (r. flank), spinal cord, spleen, sternum with bone marrow, stomach, testis (L+R), thymus, thyroid, parathyroid, trachea, uterus, voluntary muscle and abnormal tissue.

All other tissues were fixed and kept for future reference.

Hepatic aminopyrine-N-demethylase activity (APDM) was determined from the livers of 6 male and 6 female predesignated animals. Statistical analyses were conducted on cumulative bodyweight gains, weekly and total food consumption, food utilization, biochemical and hematological data, organ weights, APDM activity and other appropriate measurements.

RESULTS:

All rats survived the study and no treatment related clinical observations were noted during the study. Body weight gain was significantly reduced for both sexes at the highest dose level. It was also reduced for the 10 and 50 ppm males for week 1. In females, bodyweight gain was slightly reduced for the lowest dose group but not for the mid-dose group. Food consumption was reduced in both sexes at the highest dose level throughout the study and in males at 50 ppm during week 1. In females, there was a slight reduction in food consumption for the 10 ppm group. There was also a small statistically significant reduction in the efficiency of food utilization for females at the 250 ppm level for weeks 1 to 4 and for overall.

Sporadic significant differences in hematologic values of treated versus control groups were noted, but were not considered to be of biological significance. ALT activity was significantly reduced for the 250 ppm males after 4 weeks. ALP activity was also significantly reduced for the 250 ppm females after 13 weeks. Plasma triglycerides were reduced for the 50 and 250 ppm males after 4 and 13 weeks, but was statistically significant only for the 250 ppm males. A small, but significant decrease in urine volume was observed at 4 weeks in the 250 ppm males.

No treatment related changes were noted in the ophthalmologic examinations. A significant increase in liver weights was observed for both sexes fed 250 ppm and for males fed 50 ppm. Ovary weights were higher for all treated groups, but significant only at the 250 ppm level. However, all values were within the historical control range.

The activity of hepatic APDM was significantly increased in both sexes fed 250 ppm and in males fed 50 ppm. No treatment related macroscopic or microscopic changes were noted at termination of the study.

DISCUSSION:

This was a well conducted study. There was a significant reduction in body weight gain and in food consumption at the highest dose level (250 ppm). The authors suggested that since in males the bodyweight gain continued to diverge from that of the controls, this was a continuing toxic effect rather than a palatability problem. In actuality, the data are borderline. The reduction in food consumption and bodyweight gain at the highest dose level could be due to lack of palatability of the diet. The reduction in ALT and ALP activities and triglyceride levels support the possibility of slight starvation of the animals. The authors also stated that the increase in liver weights and in APDM activities were indicative of an adaptive response. This is likely to be the case. Other similar insecticides have been known to induce liver

enlargement as an adaptive response (e.g. pyrethrum (85 mg/kg/day in the rat)). These results were supported by the results of the subchronic study conducted on rats with cyhalothrin, of which PP321 is the resolved enantiomer pair. In that study, the increase in APDM was also considered to be adaptive. The NOEL for this study is considered to be 50 ppm, which is also the NOEL for the cyhalothrin subchronic study in rats.